Remarks

In the Office Action dated May 27, 2003, claims 17-28 and 41-47, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-48 have been canceled and new claims 49-66 have been added to the application.

In order to clarify the status of prior claim amendments, all of the pending claims have been canceled and new claims which are believed to correspond to the pending claims, as previously amended, have been added to the application. No new limitations have been added to the claims, the cancellation of the prior claims and the addition of new claims is simply to clarify the status of prior claim amendments.

The office action indicates that the Brief Explanation of the Drawings should refer to the multiple views shown in some of the drawings. The specification has been amended to reference these views.

The office action indicates that amendments shown in the marked up copy of claims 42, 43 and 47 were not included in the directions to amend the claims. In order to clarify this issue and the status of all prior claim amendments, claims 1-48 have been canceled and corresponding claims 49-66 have been added to the application.

Since Celeste is the main reference relied on in all of the rejections and is cited as support for the contention that shortened forms of MP52 are expected to have activity, all of the rejections will be addressed together. Claim 17 was

rejected under 35 USC §103(a) as unpatentable over Celeste in view of Ben-Bassat, Hirel and Georgiou in view of Tonouchi and Thompson. Claims 17 and 18 were rejected under 35 USC §103(a) as unpatentable over Celeste in view of Ben-Bassat, Hirel and Georgiou in view of Tonouchi and Thompson further in view of Hotten and Cerletti. Claims 17-28 and 41-47 were rejected under 35 USC §103(a) as unpatentable over Celeste in view of Ben-Bassat, Hirel and Georgiou in view of Tonouchi and Thompson further in view of Hotten and Cerletti and further in view of Neidhardt. Applicants respectfully point out that Celeste was not able to show activity for MP52, even though his test conditions worked for BMP's (e.g. BMP-4/BMP-2 subgroups worked under the chosen test conditions), and therefore Celeste assumed that MP52/GDF-5 does not have the same activity. In view of this failure to show activity, one skilled in the art would not reasonably believe that the shorter fragments, which are indicated by Celeste, would show sufficient application *in vivo*. In the article, it is shown that BMP-4 has a high proportion of basic amino acids within the N-terminus region before the 7-cysteine region. By deleting said regions (three amino acids, which consecutively follow one another are sufficient), it can be shown that these amino acids are important in order to avoid a too far-reaching diffusion of BMP-4, which is achieved by the interaction with the extracellular matrix (ECM). Applicants point out that MP52 also possesses a high proportion of basic amino acids in the short N-terminus region before the 7 cysteine region (basic amino acids are marked: APLAT**R**QG**KR**PS**K**NL**K**A**R**C). Thus, one could also expect that MP52 would interact with the ECM. With the induction of cartilage or bones, it is

important that BMP and/or MP52 remains where the cartilage and/or bone shall arise, i.e. that it is only released slowly and does not diffuse immediately (a mode of action as "short range signal" is also important in the bone region since bones should only be induced at particular positions). As indicated in the office action, by referring to the Spiro article, a synergy between GDF-5/MP52 and components of ECM arises. By the omission or decrease of interactions with the ECM *in vivo*, it is not foreseeable what unphysiologically high concentration of MP52 would be necessary in order to obtain a clinically reasonable effect in a patient at the site where the cartilage and or bones should be induced. In other words, one skilled in the art would believe that deleting basic amino acids within the N-terminus region before the 7-cysteine region would result in decreased interactions with the ECM *in vivo.* Decreased interactions with the ECM could mean that higher concentrations of MP52 would need to be administered. Celeste does not suggest or disclose what should be considered with regard to the matrix and/or the application site or the dosage in order to have cartilage-and bone-inducing activity with an MP52 fragment that starts with amino acid 17 or 19 (i.e. without the accumulation of the basic amino acids). For *in vivo* activity, not only is the intrinsic activity of the protein (MP52) necessary but the protein must remain at the site long enough produce the desired effect. Even if the skilled artisan assumed that the shortened fragments would maintain the same activity, which is not clear in view of Celeste) it was not predictable that the shortened fragments would remain at the site long enough *in vivo.* Therefore, the statement in the office action that "*Celeste is evidence that one of ordinary skill in the art*

would reasonably expect that the shortened forms of MP52 do retain the biological activity of the non-shortened forms" is untenable. Such an assumption cannot be made since Celeste did not know what individual regions or amino acids were necessary (e.g. the effect of the accumulation of basic amino acids was not known yet). Moreover, single regions (e.g. regions for the interaction with ECM and therefore local limitation of the protein) can be important for some applications but not for other applications (i.e. applications for which localization of the protein is probably not necessary). Celeste provides only assumptions without providing a clear teaching on how cartilage- and bone-inducing activity (he was obviously not successful with his test conditions) can be induced as well as what must be considered, if shorter fragments are used for cartilage and bone induction. Thus, a considerable effort would be required for a person skilled in the art to determine the conditions required for cartilage- and bone-inducing activity *in vivo* for MP52, especially for shortened MP52 fragments.

Applicants also point out that the previously submitted Ohkawara article (see page 208) indicates that a transformation to include a "short signal molecule" with activin ß, which normally does not have an accumulation of basic amino acids, was attempted by inserting basic amino acids or replacing them by others. This however *"significantly diminished its biological potency"*. In addition, page 206 of Ohkawara indicates that their results "led us to propose that the basic amino acids in the N-terminal region of BMP-4 and, particularly, the RKK residues play an essential role in conferring on BMP-4, a short range action in the animal cap". As pointed out on page 5 of the office action, Spiro indicates

that the "synergy demonstrated between components of the ECM and the response to rhGDF-5 can be expected to have a direct impact on the activity and efficacy of matrix/rhGDF-5 combinations in tissue-grafting indications". Thus, one skilled in the art would not assume that changes can generally be made at the N-terminus without affecting interaction with the ECM and thus changing the activity. In other words, some changes at the N-terminus may change the activity and others may not. Therefore, broad assumptions cannot be made regarding changes at the N-terminus and biological activity.

In summary, though Celeste suggests that shortened MP52 fragments would retain activity, Celeste was unable to show such activity. In view of the above discussed references (Ohkawara and Spiro), one skilled in the art would believe that deleting basic amino acids within the N-terminus region before the 7-cysteine region would result in decreased interactions with the ECM *in vivo* resulting in less localization and insufficient *in vivo* activity. None of the remaining cited references indicate that the shortened MP52 fragment will retain the desired *in vivo* activity and thus applicants request that these rejections be withdrawn.

Applicants respectfully submit that all of claims 49-66 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an

extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

By _____

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